

# ***Issues Surrounding Genetic Testing***

## **Public Health Assessment of Genetic Tests for Screening & Prevention**

**September 26, 2004**

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# Why Is Genetic Testing a Public Health Issue?



## Diagnosis / prenatal diagnosis

Mainly rare, single-gene disorders  
Chromosome abnormalities

## Newborn screening

## Other population-based applications

Carrier detection  
Predictive testing  
Pharmacogenomics

**Potential for broad  
public health impact**

# *ASHG Statement on Cystic Fibrosis Screening - 1990*

- Offer carrier testing to couples with family history
- Pilot programs - gather more data on laboratory, educational, & counseling aspects of screening
- Address quality control in labs conducting tests
- Begin large-scale population screening when
  - the test detects a larger proportion of CF carriers
  - more information is available on issues surrounding the screening process

Routine CF carrier testing of pregnant women and other individuals is NOT yet the standard of care in medical practice

# *Institute of Medicine*

## Committee on Assessing Genetic Risks

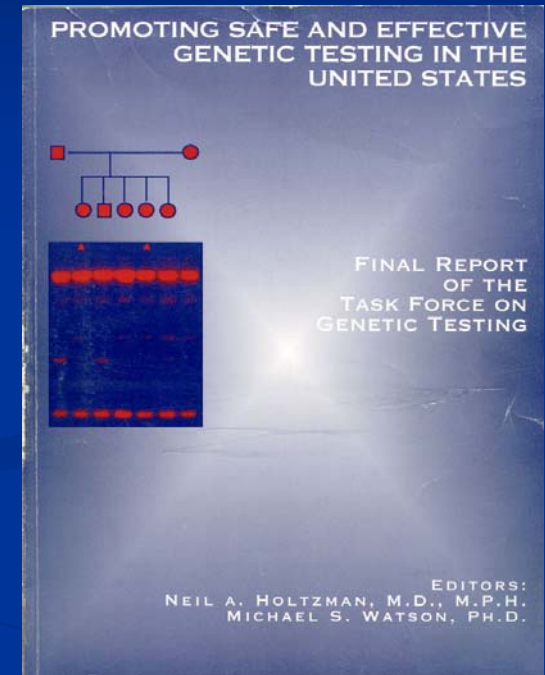
- 1994 Report: *Assessing genetic risks: Implications for health and social policy*
- Concerns raised:
  - Imperfect predictability of tests
  - Quality of labs providing clinical genetic tests
  - Lack of proven interventions for many disorders
  - Limited ability of many health care providers to explain genetic tests accurately and in a non-directive manner

# *NIH-DOE Task Force on Genetic Testing*

- Launched April, 1995 to examine questions about genetic testing:
  - How will safety, effectiveness, and correct interpretation be ensured?
  - How accurate is genetic testing at identifying mutations?
  - How reliable is a positive test result as a predictor of disease?
  - How will the quality of laboratories providing the tests be ensured?
  - What are the psychological effects of genetic testing?
  - What counseling services are needed for informed decision-making?

# *NIH-DOE Task Force on Genetic Testing*

- “For the most part, genetic testing in the US has developed successfully...”
- Evidence-based entry of new genetic tests into clinical practice
- The need to monitor laboratory performance



# *NIH-DOE Task Force on Genetic Testing*

## Proposed definition of a 'genetic test'

“Analysis of DNA, RNA, proteins and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes.”

# *NIH-DOE Task Force on Genetic Testing*

- Proposed assessment criteria
  - Analytic validity must be determined before entry into clinical practice
  - Data to establish clinical validity must be collected
    - Independently replicated and peer reviewed
    - Study sample representative of population to be tested
  - Before general acceptance in clinical practice, data must demonstrate benefits & risks (clinical utility)
- Raised issue of direct-to-consumer marketing
- Calls upon the Secretary HHS to establish an advisory committee on genetic testing

# *Secretary's Advisory Committee on Genetic Testing*



- Convened in June, 1999
- Assess, in consultation with the public, the adequacy of current oversight of genetic testing
- Major issues addressed included:
  - Reviewing the options for oversight of genetic tests
  - Determining the process that should be used to collect, evaluate and disseminate data on tests
  - Selecting criteria for assessing the benefits and risks of tests

# *Secretary's Advisory Committee on Genetic Testing - 2001 Report*



- Confirmed Task Force criteria
- Added emphasis on “social issues” (ELSI)
- Encouraged collaboration between labs & Dept of Health & Human Services agencies to
  - facilitate data collection
  - provide information to providers & consumers
- Recommended
  - review of new genetic tests by FDA prior to marketing
  - augmenting Clinical Laboratory Improvement Act (CLIA) to ensure quality of genetic testing laboratories

# *Secretary's Advisory Committee on Genetic Testing*



## Proposed definition of a 'genetic test'

“... an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes.”

## *More recently*

**2003** SACGT disbanded

Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)

Help address complex medical, ethical, legal and social issues raised by the application of new genetic technologies

**2004** Notice of Proposed Rule Making for Genetic Testing Specialty under CLIA

Professional organizations, FDA, other agencies, and regulatory groups continue to consider their roles in evaluation and oversight of genetic testing

# *Genetic testing issues*

- Translating research to quality testing in clinical practice
- Providing information on appropriate use to providers, policy makers and the public
- Monitoring use and ensuring appropriate quality and access
- Addressing complex social issues
- Maintaining adequate oversight



# Genetic tests: Current US oversight

## Food and Drug Administration (FDA)

- Regulates test kits as *in vitro* diagnostic devices (IVDs)
  - Premarket review to assess accuracy & clinical sensitivity/specificity
- Most genetic testing does not use commercial test kits
  - Two kits currently have FDA approval
- FDA has not regulated tests as clinical services, but regulation remains an option
- Controls ASRs (Analytic Specific Reagents) as medical devices
  - Good Manufacturing Practices, distribution, labeling
  - Laboratory responsible for validation

# *Genetic tests: Current US oversight*

## Centers for Medicare & Medicaid Services

- Regulate all clinical laboratory testing performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA)
- Laboratories develop clinical genetic tests under “home brew” regulations
  - Developed in house and marketed as clinical laboratory services
  - Labs responsible for analytic & clinical validation of tests
- Address personnel qualifications, quality control, proficiency testing

# *Genetic tests: Current US oversight*

## State laws

- New York Clinical Laboratory Evaluation Program – process that oversees validation and approval of molecular tests

## Professional organizations

- Clinical & laboratory practice guidelines
  - Expert opinion ± systematic evidence review

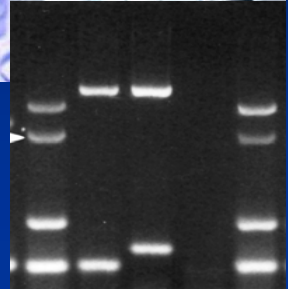
# *Public health assessment of genetic testing*

Evidence-based evaluation needed at two key points:

- Transition from research to clinical practice
  - Evidence-based review to establish safety and efficacy before widespread use
- Post-implementation period
  - Demonstrate acceptable performance in practice
  - Assess implementation success and public health impact

# *Transition to clinical practice*

- Collect and analyze data
  - Establish test performance
  - Begin assessment of benefits and risks
    - Avoid conflicts of interest
- Determine availability of needed facilities and resources
- Identify ethical, legal & social issues
- Develop plans for quality assurance, provider and consumer education, monitoring performance in practice
- Determine what we know and what we don't know



# *Transition to clinical practice*

- Summarize and disseminate findings
  - Educate providers & consumers
    - Realistic expectations
    - Appropriate use of tests
  - Guide policy development
    - Move from expert opinion to evidence-based review as a basis for practice guidelines & recommendations
  - Identify research priorities

# *Genetic testing: Different than non-genetic testing?*

- Genetic information
  - May predict future health status
  - Can divulge information about family members
  - Can be used to discriminate/stigmatize
  - Can cause psychological harm
- Genotyping may only be done once
- Increased awareness of genetic testing and public perception that is “different”
  - Call for action

# *Genetic testing:*

## *Different than non-genetic testing?*

- Evaluation process is the same
- “Handle with caution” (Green & Botkin, Ann Int Med, April 2003) any test that
  - Identifies a stigmatizing disease
  - Provides results that substantially affect family members
  - Identifies a disorder/condition for which there are no acceptable and effective treatments/actions
  - Has complex results that are difficult for clinicians to interpret

## USPSTF

## ACCE Model

### Goals

Assess merit of preventive measures (screening tests)  
Identify research agenda

Evaluate genetic tests before transition into clinical practice  
Identify gaps in knowledge

### Methodology

Analytic framework with key questions that link preventions with outcomes  
Outcome tables on benefits and harms  
**Focus on clinical utility**

44+ targeted questions on ACCE elements plus disorder/ setting  
Collect, analyze, summarize data using tables & graphics  
**Broader focus – “first look” at all elements**

### Grading Quality of Evidence

**Structured approach** for inclusion/exclusion

**Ad hoc approach** for extracting maximum information

### Product

**Specific recommendations** about use in primary care

**Review & interpret data without suggesting policy**

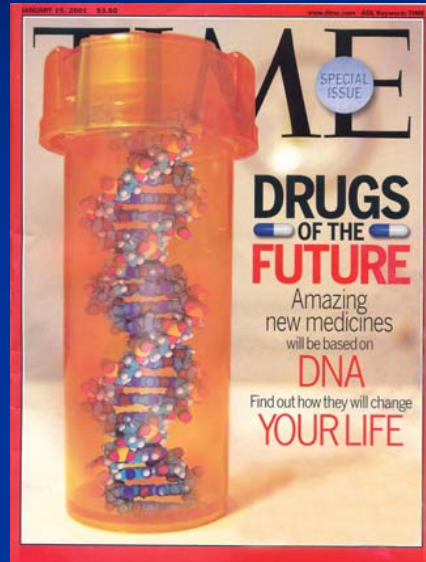
# *International health technology assessment (HTA)*

|                   |   |
|-------------------|---|
| Australia         | Medical Services Advisory Committee   |
| Canada            | Health Canada<br>Canadian Coordinating Office for Health<br>Technology Assessment (CCOHTA)<br>Agence d'évaluation des technologies et des<br>modes d'intervention en sante (AETMIS) |
| Denmark           | Danish Centre for Evaluation & HTA  |
| France            | Agency for National Accreditation & Evaluation in<br>Health   |
| New Zealand       | New Zealand HTA Clearing House  |
| United<br>Kingdom | National Coordinating Centre for HTA  |

HTAi Health Technology Assessment International

INAHTA International Network of Agencies for HTA

# Expectation vs Hype



# *Genomics in medical practice in 2010?*

*Results of genetic testing in a hypothetical patient*

| Condition       | Genes                  | RR  | Lifetime |
|-----------------|------------------------|-----|----------|
| Prostate cancer | <i>HPC1, 2, 3</i>      | 0.4 | 7%       |
| Alzheimer's     | <i>APOE, FAD3, XAD</i> | 0.3 | 10%      |
| Heart disease   | <i>APOB, CETP</i>      | 2.5 | 70%      |
| Colon cancer    | <i>FCC4, APC</i>       | 4.0 | 23%      |
| Lung cancer     | <i>NAT2</i>            | 6.0 | 40%      |

*Adapted from:* Collins FC, New Engl J Med 1999;341:28-37.

# Genomics in medical practice in 2004?

Great Smokies Diagnostic Laboratory

[www.genovations.com/profiles.html](http://www.genovations.com/profiles.html)

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### Genovations™ Profiles

#### CardioGenomic™ Profile

Identifies genetic single nucleotide polymorphisms associated with increased risk of developing atherosclerosis, hypertension, and coronary artery disease. Risk factors include methylation defects, hyper-coagulation syndromes, cholesterol regulation defects, inflammation, general risk markers and cardio-protective markers.

#### OsteoGenomic™ Profile

Identifies genetic single nucleotide polymorphisms associated with increased risk of developing osteopenia and osteoporosis. Risk factors include collagen synthesis, calcium metabolism, vitamin D3 activity, parathyroid hormone action, osteoclastic activity, and chronic inflammation.

#### DetoxiGenomic™ Profile Now Available

Identifies genetic single nucleotide polymorphisms associated with increased risk of developing detoxification defects especially with increased exposure to xenobiotics and other toxins. Risk factors include altered cytochrome P-450 activity in phase 1 detoxification, impaired glutathione conjugation and acetylation in phase 2 reactions, altered catecholamine methylation and increased oxidative stress. Detoxification defects have been associated with increased risk for certain cancers, chronic fatigue, multiple chemical sensitivity, and alcoholism.

#### ImmunoGenomic™ Profile

Identifies genetic single nucleotide polymorphisms associated with increased risk of developing defects in immune competence and surveillance. Risk factors include altered interleukin production and activity within the body and increased production of other cytokines like tissue necrosis factor alpha that may lead to conditions characterized by chronically up-regulated inflammatory response. Immunologic polymorphisms have been associated with increased risk of asthma, atopy, osteopenia, heart disease, and infectious diseases.

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# Cystic fibrosis carrier testing

## Preconception & Prenatal Carrier Screening for CF

### Description

Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines

This manual offers guidance for ob-gyns and other health care providers on the candidates for cystic fibrosis carrier screening, screening strategies and process, laboratory testing for carrier screening, and counseling for screening.

Item #CF003

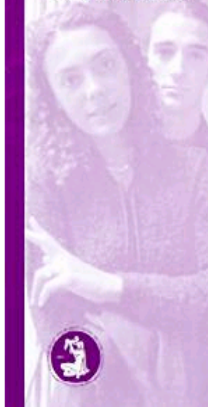
Price: \$15

ACOG members: \$9

2001

ISBN

### Cystic Fibrosis Carrier Testing: *The Decision Is Yours*



This booklet was prepared to give you information about cystic fibrosis (CF) and CF carrier testing. Carrier testing is being made available to you on a voluntary basis. Testing can be right for some people and not right for others based on many factors. These include your level of risk, your family situation, plans and needs, and your religious and spiritual beliefs. Whether or not you are tested is a personal decision that belongs to you and your baby's father. Before deciding, you should read this booklet so you understand what CF is and what carrier testing is about. On page 9 of this booklet, there is space for you to write down any questions you may have.

If, after reading the booklet, you want to be tested, or simply want to know more about the test, you should tell your health care provider that you are interested in learning more about CF carrier testing. You may also want to check to make certain that the cost of CF testing is covered by your insurance company.

## ACOG NEWS RELEASE

For Release: Embargoed until December 12, 2001  
9:00 AM EST

### Ob-Gyns Offering Large-Scale Cystic Fibrosis Screening *Represents First Major Clinical Change from the Human Genome Project*

Washington, DC -- The nation's obstetrician-gynecologists have initiated one of the first clinical changes in the US arising from discoveries of the human genome project. In recent weeks, ob-gyns began to greatly expand the number of couples offered genetic screening for cystic fibrosis (CF) during preconception or prenatal care, thanks to tests made possible by genetic research.

"The genetic revolution has begun," announced Michael T. Mennuti, MD, of The American College of Obstetricians and Gynecologists (ACOG), speaking today at an ACOG press briefing in New York City. "The advances of the human genome project have moved from the laboratory to the obstetrician's office. With these changes come new options and new decisions for expectant couples."

ACOG now recommends that ob-gyns make DNA screening for cystic fibrosis available to all couples seeking preconception or prenatal care — not just those with a personal or family history of CF. ACOG has distributed physician and patient education materials to help implement this major screening

gene would have a 1 in 4 chance of delivering a child with CF and gastrointestinal symptoms of varying severity, stunted growth and shortened lifespan and require intensive medical care.

# BRCA 1/2 Testing

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Discover the risks. Understand the options.

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- Mutation Prevalence Tables



There are patients in your practice who may have up to a 100%<sup>26</sup> chance of developing hereditary cancer. Find out how to identify and manage these high-risk patients.

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Learn about genetic testing for hereditary colorectal cancer.



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# Alternative for colorectal cancer screening

## PreGen-Plus™ Non-Invasive Colorectal Cancer Screening

### The Best Test Is the One That Gets Used

- Only 37% of colorectal cancers are detected at an early stage, when most treatable.<sup>1</sup>
- At least 60% of the 80 million Americans over the age of 50 have never been screened.<sup>2</sup>
- 30,000 lives could be saved annually if colorectal cancers were detected at an early stage.<sup>3</sup>

The Best Test Is the One That Gets Used



**PreGen Plus™**  
Keep It Simple. Catch It Early.<sup>SM</sup>

[Click to View Flash Demo](#)

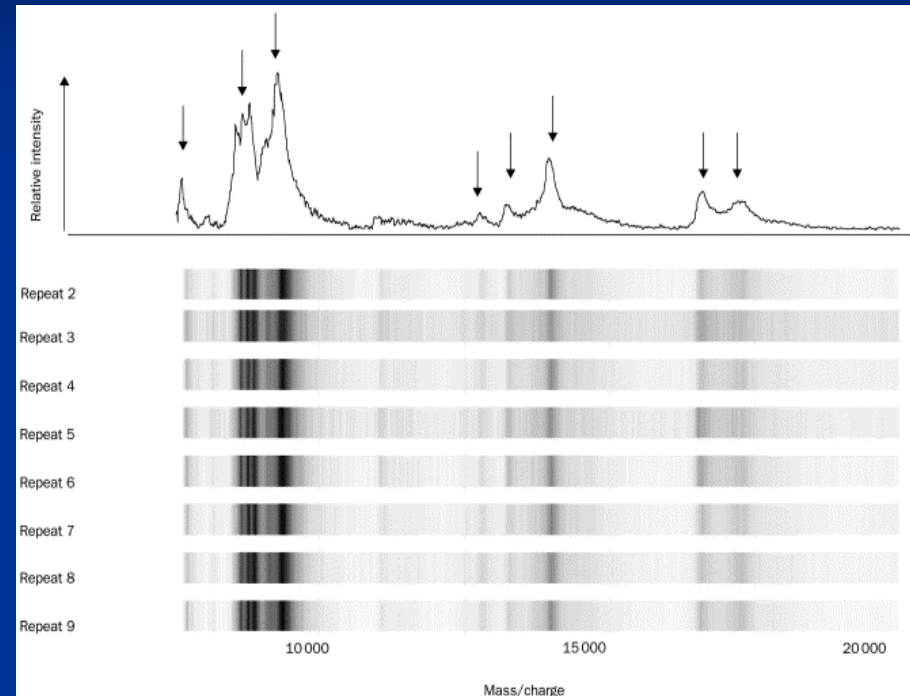
LabCorp is pleased to announce the availability of PreGen-Plus, a non-invasive test designed to detect clinically significant colorectal neoplasia (invasive cancer and advanced adenomas). PreGen-Plus is intended for use in asymptomatic patients 50 years of age and older who are at average risk of developing colorectal cancer.\*

PreGen-Plus is Simple and Non-Invasive



# *Diagnosing ovarian cancer by proteomics*

- Patterns of specific serum proteins can be used to detect OvCa, even in early stages
- Clinical trials in progress
- FDA review will follow
- “OvaCheck” technology & interpretive software licensed
- Scheduled to be offered in 2004



Petricoin EF. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet*. 2002 Feb 16;359(9306):572-7.

# Susceptibility test for addictive behavior



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Are you compulsive? Have you ever wondered why you crave certain things in an irrational manner? Would you like to know if you have the genetic predisposition to drugs and alcohol? Are you concerned about your children's future? Does your child have the genetic trait that leads to disruptive and addictive personalities? DNA testing can help you to understand and manage a child's behavior before it gets out of control.

Imagene will test a panel of dopaminergic related Reward Deficiency Syndrome. This will allow you to know if there is a genetic predisposition towards any addictions. The Reward product line is then available to treat the genetic predisposition towards RDS.

Imagene is an at home genetic testing kit that is simple to use. Here are the instructions.

1. Take Foam tipped applicator and rub the inside of left cheek 25 times. Repeat with second applicator.
2. Take foam tipped applicator and rub inside of right cheek 25 times.
3. Take applicator and place inside circle of the indicator card.
4. Press and hold for 1 minute.
5. Flip and reverse Applicator and repeat step 3 within the same circle of the indicator card.
6. The pink circle turns white when the test is complete.

“Are you concerned about your children’s future? Does your child have the genetic trait that leads to disruptive and addictive personalities? DNA testing can help you to understand and manage a child’s behavior before it gets out of control.”



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